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Myocardial Salvage Imaging: Where are We and Where are We Heading?

A Cardiac Magnetic Resonance Perspective.

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Abstract

Purpose of review: cardiac magnetic resonance (CMR) has emerged in recent years as a reliable tool to assess, in a single examination after a reperfused myocardial infarction, the initially area at risk (AAR), the final infarct size (IS) and from their difference the salvaged myocardium (SM). The aim of the present review is to summarize recent advances in the CMR imaging of SM.

Recent findings: while there is consensus on the use of late gadolinium enhancement (LGE) to calculate IS, how to assess the AAR is a debated topic. The use of T2 weighted short-TI inversion recovery (T2W-STIR) is to date supported by a large amount of data, but it is affected by several limitations. Newer techniques have been developed to overcome T2W-STIR limitations, some of them have been already used in randomized clinical trials (RCTs) while others are showing promising results. The use of CMR to generate surrogate endpoints in RCTs is gaining attention; in this context, analyses of data from recent RCTs suggests that the assessment of SM as outcome measure could be useful to reduce sample sizes and costs of trials.

Summary: CMR is a reliable technique for the assessment of SM. LGE is the gold standard for IS measurement, while which is the best technique for the evaluation of AAR is still debated. When using CMR-derived endpoints in RCTs, the assessment of SM is advisable.

Keywords: Cardiac Magnetic Resonance; Myocardial Infarction; Area at Risk; Infarct Size; Salvaged Myocardium; Clinical Trials.

Introduction

The complete occlusion of a coronary artery initially generates a reversible myocardial injury within the vascular bed supplied by the occluded vessel. Subsequently, a necrotic injury starts to develop from the subendocardial layer, reaching within hours the epicardial layer in what has been called the "wavefront phenomenon" [1]. A prompt reperfusion interrupts the progression of the necrotic wavefront, leading to a salvage of a certain amount of myocardium that is ischemic but still not necrotic [2]. Since in the absence of an external intervention these cardiomyocytes would have been reached by the spreading of the necrosis, they have been referred to as salvaged myocardium (SM), while the initially ischemic area, as area-at-risk (AAR). The visualization of SM offers the opportunity to gain an insight into the mechanisms of myocardial damage after ischemia and reperfusion. By the histologic measurement of SM in animal models it was possible to identify several factors related to the spreading of the necrosis [2, 3, 4], acquiring information that had an impact on clinical practice. In vivo, several imaging techniques have been developed for the SM assessment, all of them relying on the assessment of the AAR and final infarct size (IS), while SM is obtained by their difference [5, 6]. Coronary angiography can be used to detect the AAR only, whereas echocardiography and cardiac computed tomography are less used for this purpose due to their inherent limitations (i.e. lack of validation, low sensibility and specificity, radiation exposure) [5]; on the other hand, single photon emission tomography (SPECT) and cardiac magnetic resonance (CMR) have been considered among the reference techniques [5]. However, although SPECT during the acute phase can be used to identify the AAR, this would require the injection of the tracer when the artery is still occluded, while the image acquisition takes place up to 8 hours after reperfusion and reflects the state of coronary perfusion before the intervention [7, 8]. The same exam should be repeated days later to detect the IS [9, 10]. The added value of CMR compared to SPECT is not only its ability to image the ischemic myocardium with a higher spatial resolution, but also the possibility to assess both AAR and IS retrospectively in a single examination [11].

Using CMR it was possible to directly assess in humans how different factors can impact the progression of the necrotic wave. In example, it was demonstrated how the duration of coronary occlusion possibly is one of the strongest determinants of SM [12]. Also, it has been previously shown that the presence of prodromal angina [13], female sex [14] and a lower heart rate at presentation [15] are all factors associated to a higher SM. Thanks to its reliability, CMR derived SM has been used as outcome measure in studies testing the effectiveness of new drugs or reperfusion strategies aiming to reduce the cardiomyocytes loss after an acute myocardial infarction [16 ••]. The present review will discuss recent advances and future perspectives in the CMR imaging of SM, with a focus on the different methods for SM imaging and on the use of SM as an end-point in clinical trials.

Measuring Area at Risk

The AAR is substantially the vascular bed of the occluded artery, a region initially subjected to a reversible ischemic injury that gradually becomes necrotic in the absence of any treatment. The use of CMR for the assessment of AAR has animated intense debates [17, 18]. T2 based techniques are the most widely used methods for the assessment of AAR in vivo, all of them essentially relying on the augmented water content within the ischemic myocardium [19, 20]. It was argued that limits of validation studies and pathophysiologic findings may suggest that imaging of edema does not truly depicts the ischemic myocardium [17]. Nevertheless, whatever the exact functional and anatomical abnormalities depicted by the CMR imaging of AAR are, it should be finally highlighted that in this context CMR has been successfully tested in the clinical arena. Specifically, SM with T2W-STIR derived AAR quantification has been validated against SPECT [21]. It showed good correlation with microsphere-evaluated AAR in an animal model [19], was proven to have prognostic relevance [22] and has been successfully used as an outcome measure in randomized controlled trials (RCTs) [16 ••].

The following paragraphs will focus on those CMR techniques for AAR quantification already used in the setting of RCTs. Description of the older or new but promising techniques will also be provided (Table 1).

T2W-STIR. AAR is depicted by a bright signal when using T2 weighted short-TI inversion recovery sequence (T2W-STIR) [11]. The ischemia and subsequent reperfusion generates an inflammatory and edematous reaction that involves mostly the necrotic region, but also the peri-infarct zone. Consequently, it was demonstrated that the bright images obtained by T2W-STIR reflect the edematous myocardial tissue and thus both the area of reversible and irreversible injury [23]. T2W-STIR was among the first used CMR techniques for the quantification of AAR [19] and a large amount of literature has been published so far. The presence of edema by T2W-STIR in the first days after an acute coronary syndrome was able to predict mortality [24] and also the extent of SM provided prognostic information, predicting mortality and major acute cardiovascular events in studies in which T2W-STIR was used to quantify the AAR [22, 25, 26]. Consequently, in the great majority of RCTs in which SM is used as an outcome measure, AAR assessment is carried out by the use of T2W-STIR (Appendix 1 and Supplementary Table 2). However, the technique has many limitations. T2W-STIR imaging of the AAR is characterized by a low contrast between diseased and normal regions [17]. As a result, when compared with other techniques, T2W-STIR is affected by a higher interobserver variability [27 •]. Moreover, motion artifacts and slow-flow artifacts [28] can affect the quality of the images and prevent an appropriate interpretation of data. This eventuality ranges from only 5% of the examinations when considering a single center with high expertise [27], rising to 40% when analyzing multicenter data from RCTs [29]. This issue should be taken into account when measuring AAR with T2W-STIR. Another controversial point is which method should be used to measure the bright edematous area depicted by T2W-STIR. The 2 standard deviation (2SD) method has been initially suggested [11]. However, different techniques have been used both in validation studies (i.e. 2SD [30] and manual contouring [21]) and in RCTs (see Supplementary Table 2). In this context, a recent research found that manual contouring

provides the lowest variability (intraobserver, interobserver and interscan) when compared to 6 other methods [31 •]. However, it should be highlighted that this study was carried out in a single center with a high expertise in the technique.

T2 mapping. Assessment of the AAR can also be carried out using T2 mapping. This recently developed technique uses T2-prepared steady state free precession sequences to enable a quantitative detection of edema, overcoming some of the T2W-STIR related limitations [32]. T2 mapping has been validated in an animal model against the microsphere evaluated AAR [33]. In vivo, it was compared with SPECT, showing good agreement with the extent of AAR as determined by nuclear imaging with a grade of correlation comparable to T1 mapping and possibly better than T2W-STIR [34]. When compared to T2W-STIR, T2 mapping enables the acquisition of images with a higher diagnostic quality and the detection of the AAR with a higher sensibility [35]. This technique was also proven to be the most reproducible method for the assessment of the AAR and it was described as a less user-dependent technique with a smaller learning curve [27 •]. For these reasons, T2 mapping is emerging as a robust technique for the quantification of AAR. It has been used as reference technique in studies that tested newer CMR sequences for the evaluation of AAR [36 ••] and also for AAR quantification in RCTs that used SM as outcome measure [37]. However, data on prognosis are still lacking.

CE-SSFP. Contrast-enhanced steady-state free precession (CE-SSFP) generates images that are dependent on T2/T1 ratio [38] and can be used to visualize the AAR that appears brighter than the remote myocardium [39]. The reasons of this phenomenon are not completely understood. During a myocardial infarction, an increased distribution volume takes place also in reversibly injured myocardium [40, 41] and this would probably affect also the distribution of gadolinium contrast media, leading to an increased signal within the AAR [42]. CE-SSFP for the imaging of AAR has been validated against SPECT [39] and performed well when compared to T2W-STIR [42]. More recently, CE-SSFP was used to quantify AAR and calculate SM in 2 large RCTs [43, 44]. Analyses

of data from these 2 trials showed that CE-SSFP had a good agreement with T2W-STIR in the quantification of AAR and in the identification of the culprit artery. Interestingly, a lower number of exams had a non-diagnostic value with CE-SSFP (6%) rather than with T2W-STIR (40%) [29]. CE-SSFP for the imaging of AAR is a more recent technique than T2W-STIR, thus less data is available (i.e. prediction of prognosis). Moreover, a comparison with newer techniques such as T2 mapping and T1 mapping is missing.

Other techniques. Among other techniques available for the assessment of the AAR, T1 mapping by the use of modified look-locker inversion recovery (MOLLI) sequences has emerged as one of the most promising both in animal models [33] and in vivo [45]. It was validated against SPECT, performing well when compared to data provided by the nuclear imaging [34]. AAR quantification by T1 mapping has been validated also against T2 mapping, showing a very high correlation [45]. Notably, it was proposed that using native and post-contrast T1 mapping it would be possible to delineate both the AAR and the IS, thus shortening the duration of the CMR examination [46]. In a recent study, pre- and post-contrast acquisition and hematocrit level were utilized to describe extracellular volume maps; through them it could be possible to differentiate the AAR and IS from the remote myocardium and to calculate SM [47 •]. Even more attractive is the observation that using different thresholds it is possible to assess both AAR and IS by the use of native T1 mapping only, without the need of contrast media administration [36 ••]; in this case, T1 maps also provided prognostic information, predicting a worse left ventricular ejection fraction and wall-thickening at a 6-month follow-up [36 ••]. Further studies are needed to extend and confirm these recent observations.

The early gadolinium enhancement (EGE) technique requires the acquisition of images early (2 minutes) after the injection of the gadolinium based contrast media. This allows to observe an area of hyperenhancement in the vascular bed of the occluded artery. The enhanced area is transmural, bigger than the final IS and it corresponds to the extent of AAR as determined by T2W-STIR [48].

A limitation to the use of EGE for the assessment of AAR is due to the high variability in relation to small changes in time of acquisition. This leads to a higher variability when compared to other techniques [31 •].

Bright-blood T2-weighted sequences (Acquisition for Cardiac Unified T2 Edema, ACUT2E) render images with a hybrid combination of T1 and T2 components [49]. It performed sufficiently well when compared to other techniques for AAR quantification [31 •] but it did not gain widespread use.

The method of the endocardial surface area (ESA) is based on the pathophysiologic assumption of the wavefront phenomenon [1, 2]. Since endocardial extension of the necrotic area is defined within 40 minutes after the coronary occlusion, the ESA method assumes that the extent of the necrotic endocardial surface, expressed as a percentage of the total left ventricular endocardial surface, reflects the AAR. An advantage of ESA method is the possibility to calculate the AAR with only one sequence (late gadolinium enhancement, LGE). However, even if it performed well against other techniques for AAR measurement [50], several limitations have been pointed out, including the risk of underestimating AAR, and subsequently SM, in patients with a small IS or with aborted infarction [51].

In summary, there is presently no clear consensus on how to measure the AAR by means of CMR. Based on the published data, it seems that the use of T2W-STIR with manual contouring, in centers with a high expertise on the technique, could reliably depict the ischemic myocardium with an acceptable rate of images with diagnostic quality. It should be also highlighted that AAR and SM quantification by means of T2W-STIR rely on a vast amount of literature data and can provide prognostic information. On the other hand, several limitations to this technique have been pointed out, and in the context of RCTs both the results variability and the optimal quality of acquired imaging in all centers are of major importance. T2 mapping and CE-SSFP seem able to overcome some of the T2W-STIR limitations and they have been both successfully used in multicenter

clinical trials. Furthermore, T2 mapping has been used as reference technique in studies validating new CMR sequences for AAR evaluation. Several other techniques are currently being tested, among them, T1 mapping appears promising. Future studies should comprehensively investigate the prognostic value of these more recent mapping techniques and their inherent limitations. In example, parametric relaxation parameters may significantly vary in relation to the machine and protocol used. Thus, normal and abnormal value ranges have not been clearly identified yet.

Measuring Infarct size

The necrotic area that results after a myocardial infarction is very well depicted by CMR [52, 53, 54, 55]. When administered in the few days after a myocardial infarction, gadolinium based contrast media enters in the irreversibly injured cells due to the cell membrane rupture [53]. This causes a reduced late wash-out and so the presence of a late enhancement (LGE). Conversely, in the chronic phase the contrast media accumulates in the collagen rich interstitium of the myocardial scar, causing an area of LGE that is usually smaller than the one measured in the acute phase [56]. Even if LGE images can provide a measure of the extent of necrosis both in the acute and chronic phase, the extent of LGE in the acute phase should be taken into account when evaluating SM. In fact, this is the measure that was proven to have prognostic relevance [22, 25, 26]. Native T1 mapping has been recently proposed as a technique to quantify myocardial necrosis and to overcome some of the critical points related to LGE imaging (i.e. image acquisition timing, post-processing and measurement method) [36 •], however LGE remains a robust parameter with a large amount of published data especially on prognosis after myocardial infarction [57], and is currently considered as the gold standard to quantify IS [58].

Limits of LGE measurement in the context of randomized clinical trials have been pointed out in a recent meta-analysis investigating 62 studies in which LGE was used as an outcome measure [59 •]. It was found that 3 different gadolinium based contrast media were used, and that this information was provided only by 69% of the pooled trials; measurement of the late enhancement area was

carried out by 7 different methods, but this information was not included in the 27% of the studies. Moreover, data about timing of the CMR examination were not always provided nor were completely uniform among the different studies. Despite all these limitations, the authors were able to propose a sample size calculation based on the IS extent in the control arms; however, they also addressed the need for a protocol standardization in order to allow an easier and more accurate comparison between different trials. In relation to this issue, it was shown that the measurement of LGE in the first days after a myocardial infarction has the lowest variability (intraobserver, interobserver and interscan) if carried out by manual contouring (performed in expert hands) when compared with 6 other techniques [31 •].

Measuring myocardial salvage

The extent of SM is given by the difference between the extent of AAR and IS. Because both are not constant after an acute myocardial infarction, the right timing to perform a CMR examination for SM assessment is a discussed topic. It was proposed that the first week after the acute event may represent an optimal and stable window for AAR evaluation [56]. Conversely, other authors hypothesized that a bimodal trend of edema is present and should be taken into account in this time period [58]; however, this hypothesis is debated and a recent large study suggested the presence of a unimodal trend of edema [61]. IS as determined by LGE decreases over time after a myocardial infarction [56]. Thus, especially in the context of a clinical trial, it is important that no significantly difference in scan day are found between groups (i.e. control and treatment arms) even considering the first week after the acute event [16 ••].

Recent data suggests that using quantitative techniques such as T1 mapping [36] and T2 mapping [62] it could be possible to discriminate between AAR, IS and remote myocardium by the use of different cut off values within the same parametric image. Further studies are needed to address this point and extend these results.

Myocardial salvage as endpoint in clinical trials

A surrogate end-point (SEP) is a laboratory or physiological marker used in substitution of a clinical end-point in RCTs. The use of a SEP enables to reduce sample size, duration and cost of a trial [63, 64]. Using CMR it is possible to assess several valid SEP, such as IS, SM and microvascular obstruction [64]. Among them, IS extent as assessed by LGE-CMR is one of the best measure for event prediction after a myocardial infarction [65]. Thus, it has been widely used as a SEP in clinical cardioprotection trials [59 •]. However, the use of IS in this setting carries several limitations to the evaluation of the truly effectiveness of a tested treatment. In fact, IS extent largely depends on factors not related to the treatment, such as the extent of AAR [66] that in turn is related to the extent of the occluded artery vascular bed [67]. In example, an individual with an extensive anterior myocardial infarction, even if treated with an early reperfusion, would have a larger AAR and IS when compared to a patient with a late reperfusion of a small right coronary artery. However, in the first case SM would be greater, since the early reperfusion makes possible for a larger part of the AAR to be spared by the necrosis: taking into account IS extent only in such a patient would not have helped in demonstrating the usefulness of the treatment. The extent of AAR and IS is related to the site of the coronary occlusion, while the extent of SM is not [15, 68]. This has important implications when projecting clinical trials in which IS is used as surrogate end-point. Moreover, to provide a balanced distribution of myocardial infarction locations between the study groups (i.e. anterior vs non-anterior myocardial infarction) it might not be enough to eliminate the discrepancies caused by differences in AAR extent. In fact, even considering only patients with an occlusion of the left anterior descending artery, the area of reversible injury may significantly vary according to the precise location of the occlusion (i.e. proximal vs mid) or the anatomy (i.e. number and size of side branches) of different individuals, as shown by angiographic risk scores of AAR prediction [69]. However, it should be highlighted that if the analyzed factor or tested treatment has a large impact on SM (i.e. time to reperfusion), all confounding factors can be overcome and a

reduction in IS can be observed [12]. On the other hand, it may happen that the impact of the analyzed factor is lower, there are significant anatomical differences between groups or the sample size is too small. In this case, the assessment of IS alone does not reveal an effect of the tested factor or treatment that actually exists (type 2 error), while an improvement of SM is still observed [15, 70]. Augmentation of sample size could be useful to overcome confounding factors related to the use of IS as outcome measure. However, in this context SM appears to be a more sensitive marker to evaluate the effectiveness of new reperfusion strategies, thus, its use could help to reduce sample sizes and costs in clinical trials, as recently demonstrated [16 ••]. A list of the main published cardioprotection trials that used SM as outcome measure is reported in the Appendix 1 and Supplementary Table 2. Some limitations inherent the use of SM as endpoint in clinical trials should be mentioned. First, to measure SM it is necessary to assess both the AAR and IS, but the evaluation of AAR is field of several debates, as mentioned before. The assessment of AAR largely relies on the edema that characterize the ischemic area, however, some tested treatments may also reduce the extent of edema, leading to an underestimation of the SM in the treated arm [34]. In conclusion, the assessment of SM owns presently the properties of a valid SEP, even if some limitations should be taken into account. When using CMR to assess SEPs in clinical trials, the measurement of SM (along with others imaging parameters) is advisable.

Conclusions

CMR is a reliable technique for the assessment of SM. LGE is the gold standard for the assessment of IS, while which is the best technique for the assessment of AAR is still debated. Increasing data are present in literature on CMR used as a method for the quantification of SEPs in clinical trials. In this case, both from a pathophysiologic and a practical point of view, the assessment of SM as outcome measure is advisable.

References

1. Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Laboratory investigation; a journal of technical methods and pathology. 1979 Jun; 40(6): p. 633-44.
2. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation. 1977 Nov; 56(5): p. 786-94.
3. Przyklenk K, Vivaldi MT, Schoen FJ, Malcolm J, Arnold O, Kloner RA. Salvage of ischaemic myocardium by reperfusion: importance of collateral blood flow and myocardial oxygen demand during occlusion. Cardiovascular research. 1986 Jun; 20(6): p. 403-14.
4. Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J, et al. Factors influencing infarct size following experimental coronary artery occlusions. Circulation. 1971 Jan; 43(1): p. 67-82.
5. Botker HE, Kaltoft AK, Pedersen SF, Kim WY. Measuring myocardial salvage. Cardiovascular Research. 2012 May 1; 94(2): p. 266-275.
6. Schelbert EB, Wong TC. Imaging the Area at Risk in Myocardial Infarction With Cardiovascular Magnetic Resonance. Journal of the American Heart Association. 2014 Aug 21; 3(4): p. e001253-e001253.
7. Kaltoft A, Bøttcher M, Nielsen SS, Hansen HHT, Terkelsen C, Maeng M, et al. Routine thrombectomy in percutaneous coronary intervention for acute ST-segment-elevation myocardial infarction: a randomized, controlled trial. Circulation. 2006 Jul 4; 114(1): p. 40-7.
8. Kaltoft A, Nielsen SS, Terkelsen CJ, Bøttcher M, Lassen JF, Krusell LR, et al. Scintigraphic evaluation of routine filterwire distal protection in percutaneous coronary intervention for

acute ST-segment elevation myocardial infarction: a randomized controlled trial. Journal of Nuclear Cardiology. 2009 Oct 12; 16(5): p. 784-791.

9. Medrano R, Lowry RW, Young JB, Weilbaecher DG, Michael LH, Afridi I, et al. Assessment of myocardial viability with 99mTc sestamibi in patients undergoing cardiac transplantation. A scintigraphic/pathological study. Circulation. 1996 Sep 1; 94(5): p. 1010-7.
10. Kristensen J, Mortensen UM, Nielsen SS, Maeng M, Kaltoft A, Nielsen TT, et al. Myocardial perfusion imaging with 99mTc sestamibi early after reperfusion reliably reflects infarct size reduction by ischaemic preconditioning in an experimental porcine model. Nuclear medicine communications. 2004 May; 25(5): p. 495-500.
11. Friedrich MG, Abdel-Aty H, Taylor A, Schulz-Menger J, Messroghli D, Dietz R. The Salvaged Area at Risk in Reperfused Acute Myocardial Infarction as Visualized by Cardiovascular Magnetic Resonance. Journal of the American College of Cardiology. 2008 Apr 22; 51(16): p. 1581-1587.
12. Francone M, Bucciarelli-Ducci C, Carbone I, Canali E, Scardala R, Calabrese FA, et al. Impact of Primary Coronary Angioplasty Delay on Myocardial Salvage, Infarct Size, and Microvascular Damage in Patients With ST-Segment Elevation Myocardial Infarction. Journal of the American College of Cardiology. 2009 Dec; 54(23): p. 2145-2153., 42.
13. Masci PG, Andreini D, Francone M, Bertella E, De Luca L, Coceani M, et al. Prodromal angina is associated with myocardial salvage in acute ST-segment elevation myocardial infarction. European Heart Journal - Cardiovascular Imaging. 2013 Nov; 14(11): p. 1041-1048.
14. Canali E, Masci P, Bogaert J, Bucciarelli-Ducci C, Francone M, McAlindon E, et al. Impact of gender differences on myocardial salvage and post-ischaemic left ventricular remodelling after primary coronary angioplasty: new insights from cardiovascular magnetic resonance. European Heart Journal - Cardiovascular Imaging. 2012 Nov 1; 13(11): p. 948-953.

15. Arcari L, Cimino S, De Luca L, Francone M, Galea N, Reali M, et al. Impact of Heart Rate on Myocardial Salvage in Timely Reperfused Patients with ST-Segment Elevation Myocardial Infarction: New Insights from Cardiovascular Magnetic Resonance. PLOS ONE. 2015 Dec 30; 10(12): p. e0145495.
16. •• Engblom H, Heiberg E, Erlinge D, Jensen SE, Nordrehaug JE, Dubois-Randé J, et al. Sample Size in Clinical Cardioprotection Trials Using Myocardial Salvage Index, Infarct Size, or Biochemical Markers as Endpoint. Journal of the American Heart Association. 2016 Mar 9; 5(3): p. e002708. *This study provides a statistical simulation based on data from 2 recent RCTs in which SM was used as outcome measure. Results from this research demonstrated the possible impact in term of reduction of sample size thanks to the use of SM rather than IS alone as outcome measure.*
17. Croisille P, Kim HW, Kim RJ. Controversies in Cardiovascular MR Imaging: T2-weighted Imaging Should Not Be Used to Delineate the Area at Risk in Ischemic Myocardial Injury. Radiology. 2012 Oct; 265(1): p. 12-22.
18. Arai AE, Leung S, Kellman P. Controversies in Cardiovascular MR Imaging: Reasons Why Imaging Myocardial T2 Has Clinical and Pathophysiologic Value in Acute Myocardial Infarction. Radiology. 2012 Oct; 265(1): p. 23-32.
19. Aletras AH, Tilak GS, Natanzon A, Hsu L-Y, Gonzalez FM, Hoyt RF, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. Circulation. 2006; 113:1865–70.
20. Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. Journal of Cardiovascular Magnetic Resonance. 2011 Feb 18; 13(1): p. 13.
21. Carlsson M, Ubachs JFA, Hedström E, Heiberg E, Jovinge S, Arheden H. Myocardium at Risk After Acute Infarction in Humans on Cardiac Magnetic Resonance. JACC: Cardiovascular Imaging. 2009 May; 2(5): p. 569-576.

22. Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G, et al. Prognostic Significance and Determinants of Myocardial Salvage Assessed by Cardiovascular Magnetic Resonance in Acute Reperfused Myocardial Infarction. Journal of the American College of Cardiology. 2010 Jun 1; 55(22): p. 2470-2479.
23. Choi SI, Jiang CZ, Lim KH, Kim ST, Lim CH, Gong GY, et al. Application of breath-hold T2-weighted, first-pass perfusion and gadolinium-enhanced T1-weighted MR imaging for assessment of myocardial viability in a pig model. J Magn Reson Imaging. 2000 May; 11(5): p. 476-80.
24. Raman SV, Simonetti OP, Winner MW, Dickerson JA, He X, Mazzaferri EL, et al. Cardiac Magnetic Resonance With Edema Imaging Identifies Myocardium at Risk and Predicts Worse Outcome in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome. Journal of the American College of Cardiology. 2010 Jun; 55(22): p. 2480-2488.
25. Masci PG, Ganame J, Strata E, Desmet W, Aquaro GD, Dymarkowski S, et al. Myocardial Salvage by CMR Correlates With LV Remodeling and Early ST-Segment Resolution in Acute Myocardial Infarction. JACC: Cardiovascular Imaging. 2010 Jan; 3(1): p. 45-51.
26. Eitel I, Desch S, de Waha S, Fuernau G, Gutberlet M, Schuler G, et al. Long-term prognostic value of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. Heart. 2011 Dec 15; 97(24): p. 2038-2045.
27. • McAlindon EJ, Pufulete M, Harris JM, Lawton CB, Moon JC, Manghat N, et al. Measurement of Myocardium at Risk with Cardiovascular MR: Comparison of Techniques for Edema Imaging. Radiology. 2015 Apr; 275(1): p. 61-70. *This study provides an interesting comparison between different techniques for AAR assessment. Variability between different operators and different scans in the same patient were tested. Finally, T2 mapping emerged as the technique with the lower variability.*
28. Abdel-Aty H, Simonetti O, Friedrich MG. T2-weighted cardiovascular magnetic resonance imaging. J Magn Reson Imaging. 2007; 26:452–459. doi: 10.1002/jmri.21028.

29. Nordlund D, Klug G, Heiberg E, Koul S, Larsen TH, Hoffmann P, et al. Multi-vendor, multicentre comparison of contrast-enhanced SSFP and T2-STIR CMR for determining myocardium at risk in ST-elevation myocardial infarction. European Heart Journal – Cardiovascular Imaging. 2016 Jul; 17(7): p. 744-753.
30. Hadamitzky M, Langhans B, Hausleiter J, Sonne C, Kastrati A, Martinoff S, et al. The Assessment of Area at Risk and Myocardial Salvage After Coronary Revascularization in Acute Myocardial Infarction. JACC: Cardiovascular Imaging. 2013 Mar; 6(3): p. 358-369.
31. • McAlindon E, Pufulete M, Lawton C, Angelini GD, Bucciarelli-Ducci C. Quantification of infarct size and myocardium at risk: evaluation of different techniques and its implications. European Heart Journal - Cardiovascular Imaging. 2015 Jul; 16(7): p. 738-746. *This research compared different methods for the measurement of AAR and IS from T2W-STIR and LGE images. Results suggested that, performed in expert hands, manual contouring provides the lowest variability for quantification of AAR and IS. This finding is of relevance in the search of a more standardized protocol for image interpretation in SM assessment.*
32. Giri S, Chung YC, Merchant A, Mihai G, Rajagopalan S, Raman SV, et al. T2 quantification for improved detection of myocardial edema. Journal of cardiovascular magnetic resonance 2009 Dec 30; 11(1): p. 56.
33. Ugander M, Bagi PS, Oki AJ, Chen B, Hsu LY, Aletras AH, et al. Myocardial Edema as Detected by Pre-Contrast T1 and T2 CMR Delineates Area at Risk Associated With Acute Myocardial Infarction. JACC: Cardiovascular Imaging. 2012 Jun; 5(6): p. 596-603.
34. Langhans B, Nadjiri J, Jähnichen C, Kastrati A, Martinoff S, Hadamitzky M. Reproducibility of area at risk assessment in acute myocardial infarction by T1- and T2-mapping sequences in cardiac magnetic resonance imaging in comparison to Tc99m-sestamibi SPECT. The international journal of cardiovascular imaging. 2014 Oct 2; 30(7): p. 1357-63.

35. Verhaert D, Thavendiranathan P, Giri S, Mihai G, Rajagopalan S, Simonetti OP, et al. Direct T2 Quantification of Myocardial Edema in Acute Ischemic Injury. JACC: Cardiovascular Imaging. 2011 Mar; 4(3): p. 269-278.
36. •• Liu D, Borlotti A, Viliani D, Jerosch-Herold M, Alkhalil M, De Maria GL, et al. CMR Native T1 Mapping Allows Differentiation of Reversible Versus Irreversible Myocardial Damage in ST-Segment-Elevation Myocardial Infarction: An OxAMI Study (Oxford Acute Myocardial Infarction). Circulation. Cardiovascular imaging. 2017 Aug 10; 10(8): p. e005986. *This innovative study demonstrated the ability of native T1 mapping to assess AAR and IS and to provide prognostic information after a myocardial infarction. The tested protocol does not require the administration of contrast media and shortens the duration of the CMR examination. Further studies are needed to confirm and strengthen these recent findings.*
37. White SK, Frohlich GM, Sado DM, Maestrini V, Fontana M, Treibel TA, et al. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC. Cardiovascular interventions. 2015 Jan; 8(1 Pt B): p. 178-188.
38. Caravan P. Strategies for increasing the sensitivity of gadolinium based MRI contrast agents. Chemical Society reviews. 2006 Jun; 35(6): p. 512-23.
39. Sörensson P, Heiberg E, Saleh N, Bouvier F, Caidahl K, Tornvall P, et al. Assessment of myocardium at risk with contrast enhanced steady-state free precession cine cardiovascular magnetic resonance compared to single-photon emission computed tomography. Journal of Cardiovascular Magnetic Resonance. 2010 Apr 30; 12(1): p. 25.
40. Arheden H, Saeed M, Higgins CB, Gao DW, Bremerich J, Wyttenbach R, et al. Measurement of the Distribution Volume of Gadopentetate Dimeglumine at Echo-planar MR Imaging to Quantify Myocardial Infarction: Comparison with 99m Tc-DTPA Autoradiography in Rats. Radiology. 1999 Jun; 211(3): p. 698-708.

41. Arheden H, Saeed M, Higgins CB, Gao DW, Ursell PC, Bremerich J, et al. Reperfused Rat Myocardium Subjected to Various Durations of Ischemia: Estimation of the Distribution Volume of Contrast Material with Echo-planar MR Imaging. Radiology. 2000 May; 215(2): p. 520-528.
42. Ubachs JFA, Sörensson P, Engblom H, Carlsson M, Jovinge S, Pernow J, et al. Myocardium at risk by magnetic resonance imaging: head-to-head comparison of T2-weighted imaging and contrast-enhanced steady-state free precession. European Heart Journal - Cardiovascular Imaging. 2012 Dec; 13(12): p. 1008-1015.
43. Erlinge D, Götberg M, Lang I, Holzer M, Noc M, Clemmensen P, et al. Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction. Journal of the American College of Cardiology. 2014 May; 63(18): p. 1857-1865.
44. Atar D, Arheden H, Berdeaux A, Bonnet JL, Carlsson M, Clemmensen P, et al. Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. European heart journal. 2015 Jan 7; 36(2): p. 112-9.
45. Bulluck H, White SK, Rosmini S, Bhuva A, Treibel TA, Fontana M, et al. T1 mapping and T2 mapping at 3T for quantifying the area-at-risk in reperfused STEMI patients. Journal of Cardiovascular Magnetic Resonance. 2015 Dec 12; 17(1): p. 73.
46. Bulluck H, Hammond-Haley M, Fontana M, Knight DS, Sirker A, Herrey AS, et al. Quantification of both the area-at-risk and acute myocardial infarct size in ST-segment elevation myocardial infarction using T1-mapping. Journal of Cardiovascular Magnetic Resonance. 2017 Dec 1; 19(1): p. 57.
47. • Garg P, Broadbent DA, Swoboda PP, Foley JRJ, Fent GJ, Musa TA, et al. Acute Infarct Extracellular Volume Mapping to Quantify Myocardial Area at Risk and Chronic Infarct Size on Cardiovascular Magnetic Resonance Imaging. Circulation. Cardiovascular imaging.

2017 Jul 3; 10(7): p. e006182. *This innovative study explored the potential role of extracellular volume mapping in the assessment of AAR and IS, and in the prediction of myocardial viability at follow-up; further studies with larger sample sizes are needed to strenghten this result.*

48. Matsumoto H, Matsuda T, Miyamoto K, Shimada T, Mikuri M, Hiraoka Y. Peri-infarct zone on early contrast-enhanced CMR imaging in patients with acute myocardial infarction. JACC. Cardiovascular imaging. 2011 Jun; 4(6): p. 610-8.
49. Payne AR, Casey M, McClure J, McGeoch R, Murphy A, Woodward R, et al. Bright-Blood T2-Weighted MRI Has Higher Diagnostic Accuracy Than Dark-Blood Short Tau Inversion Recovery MRI for Detection of Acute Myocardial Infarction and for Assessment of the Ischemic Area at Risk and Myocardial Salvage. Circulation: Cardiovascular Imaging. 2011 May 1; 4(3): p. 210-219.
50. Versteylen MO, Bekkers SCAM, Smulders MW, Winkens B, Mihl C, Winkens MHM, et al. Performance of angiographic, electrocardiographic and MRI methods to assess the area at risk in acute myocardial infarction. Heart. 2012 Jan 15; 98(2): p. 109-115.
51. Fuernau G, Eitel I, Franke V, Hildebrandt L, Meissner J, de Waha S, et al. Myocardium at Risk in ST-Segment Elevation Myocardial Infarction. JACC: Cardiovascular Imaging. 2011 Sep; 4(9): p. 967-976.
52. Arai AE. Magnetic resonance imaging for area at risk, myocardial infarction, and myocardial salvage. Journal of cardiovascular pharmacology and therapeutics. 2011
53. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation. 1999 Nov 9; 100(19): p. 1992-2002.
54. Fieno DS, Kim RJ, Chen EL, Lomasney JW, Klocke FJ, Judd RM. Contrast-enhanced magnetic resonance imaging of myocardium at risk: distinction between reversible and

irreversible injury throughout infarct healing. Journal of the American College of Cardiology. 2000 Nov 15; 36(6): p. 1985-91.

55. Schelbert EB, Hsu LY, Anderson SA, Mohanty BD, Karim SM, Kellman P, et al. Late Gadolinium-Enhancement Cardiac Magnetic Resonance Identifies Postinfarction Myocardial Fibrosis and the Border Zone at the Near Cellular Level in Ex Vivo Rat Heart. Circulation: Cardiovascular Imaging. 2010 Nov 1; 3(6): p. 743-752.
56. Dall'Armellina E, Karia N, Lindsay AC, Karamitsos TD, Ferreira V, Robson MD, et al. Dynamic changes of edema and late gadolinium enhancement after acute myocardial infarction and their relationship to functional recovery and salvage index. Circulation. Cardiovascular imaging. 2011 May 1; 4(3): p. 228-36.
57. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, et al. Relationship Between Infarct Size and Outcomes Following Primary PCI: Patient-Level Analysis From 10 Randomized Trials. Journal of the American College of Cardiology. 2016 Apr 12; 67(14): p. 1674-83.
58. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. Journal of Cardiovascular Magnetic Resonance. 2013 May 1; 15(1): p. 35.
59. • Bulluck H, Hammond-Haley M, Weinmann S, Martinez-Macias R, Hausenloy DJ. Myocardial Infarct Size by CMR in Clinical Cardioprotection Studies. JACC: Cardiovascular Imaging. 2017 Mar; 10(3): p. 230-240. *This study represents an overview on the use of infarct size as outcome measure in RCTs. Recommendations for standardization and sample size calculation are also provided.*
60. Carrick D, Haig C, Ahmed N, Rauhalammi S, Clerfond G, Carberry J, et al. Temporal Evolution of Myocardial Hemorrhage and Edema in Patients After Acute ST-Segment

Elevation Myocardial Infarction: Pathophysiological Insights and Clinical Implications. Journal of the American Heart Association. 2016 Feb 23; 5(2): p. e002834.

61. Stiermaier T, Thiele H, Eitel I. Early myocardial edema after acute myocardial infarction is stable and not bimodal in humans - Evidence from a large CMR multicenter study. International journal of cardiology. 2017 Nov 1; 246: p. 87-89.
62. Hammer-Hansen S, Ugander M, Hsu LY, Taylor J, Thune JJ, Kober L, et al. Distinction of salvaged and infarcted myocardium within the ischaemic area-at-risk with T2 mapping. European Heart Journal - Cardiovascular Imaging. 2014 Sep 1; 15(9): p. 1048-1053.
63. Desch S, Eitel I, de Waha S, Fuernau G, Lurz P, Gutberlet M, et al. Cardiac magnetic resonance imaging parameters as surrogate endpoints in clinical trials of acute myocardial infarction. Trials. 2011 Dec 14; 12(1): p. 204.
64. Bainey KR, Patel MR, Armstrong PW. Evaluation of Cardiac Magnetic Resonance as a Surrogate in ST-Segment Elevation Myocardial Infarction. The American journal of cardiology. 2015 Jun 1; 115(11): p. 1607-14.
65. Wu E, Ortiz JT, Tejedor P, Lee DC, Bucciarelli-Ducci C, Kansal P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. Heart. 2008 Jun 1; 94(6): p. 730-736.
66. Reimer KA, Jennings RB, Cobb FR, Murdock RH, Greenfield JC, Becker LC, et al. Animal models for protecting ischemic myocardium: results of the NHLBI Cooperative Study. Comparison of unconscious and conscious dog models. Circulation research. 1985 May; 56(5): p. 651-65.
67. Schelbert EB, Hsu LY, Anderson SA, Mohanty BD, Karim SM, Kellman P, et al. Late Gadolinium-Enhancement Cardiac Magnetic Resonance Identifies Postinfarction Myocardial Fibrosis and the Border Zone at the Near Cellular Level in Ex Vivo Rat Heart. Circulation: Cardiovascular Imaging. 2010 Nov 1; 3(6): p. 743-752.

68. Masci PG, Ganame J, Francone M, Desmet W, Lorenzoni V, Iacucci I, et al. Relationship between location and size of myocardial infarction and their reciprocal influences on post-infarction left ventricular remodelling. European Heart Journal. 2011 Jul 1; 32(13): p. 1640-1648.
69. Ortiz-Pérez JT, Meyers SN, Lee DC, Kansal P, Klocke FJ, Holly TA, et al. Angiographic estimates of myocardium at risk during acute myocardial infarction: validation study using cardiac magnetic resonance imaging. European heart journal. 2007 Jul 6; 28(14): p. 1750-8.
70. Eitel I, Stiermaier T, Rommel KP, Fuernau G, Sandri M, Mangner N, et al. Cardioprotection by combined intrahospital remote ischaemic perconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA CONDITIONING trial. European heart journal. 2015 Nov 21; 36(44): p. 3049-57.